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Myeloma — Results of treatment 1986 – 1990

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SUMMARY

Sixty-nine patients with multiple myeloma diagnosed during a five year period at the Belfast City Hospital were followed until death or for a minimum of one year in a retrospective study of survival. Although the patients were unselected, survival data was found to be similar to results from trials in which patient selection had occurred. Overall median survival was thirty-two months. Median survival fell with advancing disease and was 47, 27 and 18 months for Durie-Salmon stages I, II and III respectively. Those patients presenting with a platelet count of $<100 \times 10^9/1$ had a median survival of eight months in contrast to those with a platelet count $>100 \times 10^9/1$ whose median survival was 36 months. Patients presenting in renal failure had a shorter median survival of 28 months compared to 46 months for those with normal renal function.

INTRODUCTION

Over the last 25 years a series of multicentre studies by the Medical Research Council has shown a progressive improvement in the survival of patients with multiple myeloma.[1-4] This has been achieved through an increase in the intensity of chemotherapeutic regimens and an improvement in supportive care. The outcome of any trial will be affected by the preselection of patients for the trial and may often lead to apparently significant improvement in progress.[5] The present study describes the outcome for an unselected group of patients diagnosed and treated at this hospital during a five year period with follow-up to death, or for one to five years survival.

In 1990, the most recent year for which accurate figures are available, 92 patients were diagnosed as having multiple myeloma in Northern Ireland. (Northern Ireland Leukaemia Research Fund data collection service).

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METHODS

Sixty-nine patients with multiple myeloma diagnosed in the Belfast City Hospital between 1 January 1986 and 31 December 1990 were identified using the records of bone marrow examination and protein biochemistry. Administration of chemotherapy was supervised by the staff of the haematology department. The clinical haematology charts of all the patients were analysed to determine outcome. Laboratory findings utilised for diagnosis of myeloma included plasma cell infiltration in the bone marrow greater than 5%, a paraprotein band in serum or urine, and lytic bone lesions on skeletal radiography.

Patients were staged according to the Durie-Salmon classification.[6] In stage I all of the following are present — haemoglobin >10 g/dl, normal serum calcium, normal bone structure on X-ray (or a solitary plasmacytoma only) with low paraprotein production rates [IgG <60 g/l, IgA <30 g/l, urine light chains <4 g/24 hours]. Stage III is defined by the presence of any one of the following — Hb $<8{\cdot}5$ g/dl, serum calcium $>2{\cdot}62$ mmol/l, advanced bone lytic lesions, high paraprotein production rates [IgG >70 g/l, IgA >50 g/l, urine light chains >12 g/24 hours]. Stage II are those patients between I and III. A further subclassification into subgroup a (serum creatinine <176 ug/dl) or subgroup b (serum creatinine ≥ 176 ug/dl) was also used (Table I).

TABLE I

Stage and age of patients

Stage	*No*	*Median age yr*	*Age range yr*
Ia	23 (34%)	68	39 – 83
Ib	3 (4%)	66	53 – 75
IIa	13 (19%)	67	47 – 78
IIb	3 (4%)	65	60 – 69
IIIa	16 (23%)	65·5	44 – 82
IIIb	11 (16%)	68	59 – 84

Statistics

Median duration of survival was estimated by the Kaplan-Meier life table method. Univariate analysis using the log rank test was performed to identify the relationship between variables recorded at diagnosis and duration of survival. These variables included age, sex, paraprotein class, paraprotein index,[7] serum albumin level, Bence Jones proteinuria, presence of lytic lesions, β_2 microglobulin level, platelet count, serum urea level, serum creatinine level, Durie-Salmon stage and initial treatment. Cox's proportional hazard regression analysis was then used to identify those factors that were independently associated with survival. Statistical significance was taken as $p<0{\cdot}05$. Creatinine and urea values were distributed in a skewed fashion and were therefore log transformed before analysis Calculations were performed on an IBM compatible computer using EGRET software.[8] The concept of relative risk was used to compare the increased risk of death in

one category compared to a reference category; for continuous variables the change in risk associated with a one unit change in the variable is expressed.

PATIENTS AND TREATMENT

Two of the 69 patients were excluded from follow-up analysis as they moved away from the Belfast area. Of the remaining 67, 31 were male (46%) and 36 female (54%). Median age at diagnosis was 66 years for males (range 39–84 years) and 67·5 years for females (range 44–83 years). Twenty-eight patients (42%) were alive at the end of the study. The types of paraprotein were as shown in Table II.

TABLE II

Paraprotein type and relative frequency

Type	*No*
IgAK	5 (7%)
IgA λ	10 (15%)
IgGK	27 (39%)
IgG λ	13 (19%)
K only	5 (7%)
λ only	8 (12%)
Non-secretor	1 (1%)

The distribution of significant prognostic variables is compared with another unselected group of patients from Nottingham,[9] the IVth and Vth Medical Research Council myeloma trials and the US South West Oncology Group Myeloma trial (SWOG 8229)[10] and is shown in Table III. The unselected Nottingham group shows a higher proportion of patients with poorer features and shorter survival than the Belfast City Hospital group. The Belfast City Hospital and Medical Research Council trial survivals are similar, and the distribution of variables with independent prognostic significance between them was also similar, although a higher proportion of MRC patients were Durie-Salmon stage III.

Initial treatment was with melphalan and prednisolone in 22 patients; vincristine, melphalan, cyclophosphamide and prednisolone in 21; vincristine, adriamycin and dexamethasone in eight requiring aggressive therapy; melphalan alone in five; and other combination chemotherapy régimes in 6. Therapy was started if symptoms were present or there was evidence of disease progression. In general, aggressive therapy such as VAD (vincristine/adriamycin/dexamethasone) was reserved for those with advanced disease and was restricted to younger patients. Thus only one patient aged over 65 years received VAD as initial treatment and it was used in only one patient with stage I disease (who had spinal cord compression). Five patients had no treatment, two died within a month of diagnosis before chemotherapy could be given and three others have survived for intervals of 21, 40 and 44 months without chemotherapy. The diagnosis has been reviewed and confirmed in these 5 patients. Chemotherapy was withheld because of age or the presence of other illnesses, or lack of evidence of progression of myeloma. Interferon has been used in some patients during a plateau phase but it is too early to analyse its effect.

TABLE III

Patient characteristics: Clinical trial and unselected group results

	Clinical trials			*Unselected groups*	
	SWOG 8229 (%)*	MRC IV (%)*	MRCV (%)*	Nottingham (%)*	Belfast City Hospital (%)*
Haemoglobin (g/dl)					
< 7·5	4	13	11	—	6
(< 8·5)	—	—	—	(26)	(13)
7·5 – 10	20	19	24	—	30
(8·5 – 10)	—	—	—	(27)	(20)
> 10	76	68	65	47	67
Creatinine (μmol/l)					
< 130	62	59	57	50	69
130 – 200	21	22	21	20	7
> 200	17	19	22	30	24
Age (years)					
< 50	14	11	10	6	5
< 60	29	31	26	55 (50–70)	16
< 75	50	58	64	—	60
> 75	7	—	—	39 (> 70)	19
Calcium (mmol/l)					
< 2·6	—	—	—	69	81
> 2·6	—	—	—	31	19
Durie-Salmon stage					
I	3	8	5	15	37
II	19	5	9	17	24
III	78	87	86	65	39
Median survival months	29 (VCP) 48 (VMCP-VBAP)	29	24 (M7) 32 (ABCM)	25	32

V = Vincristine C = Cyclophosphamide M = Melphalan
A = Adriamycin B = Bi CNU P = Prednisolone

*percentage of each group identified by the criteria listed below.

RESULTS

Presenting features

Bone pain was the commonest presenting feature in 34 (51%) of the patients. Renal function was impaired at diagnosis in 17 (25%), and 6 (19%) presented with hypercalcaemia. Twenty-four patients (36%) had a haemoglobin level less than 10 g/dl at diagnosis. Eight patients (12%), all stage Ia, presented with features unrelated to myeloma.

Survival data

Fig 1 shows the survival curve for the study population (median survival 32 months). For males the median survival was 36 months and for females 30 months. The Kaplan Meier survival estimate at 12 months was 78% (95% confidence limits 66–86%) and at 36 months 43% (95% confidence limits 30–56%).

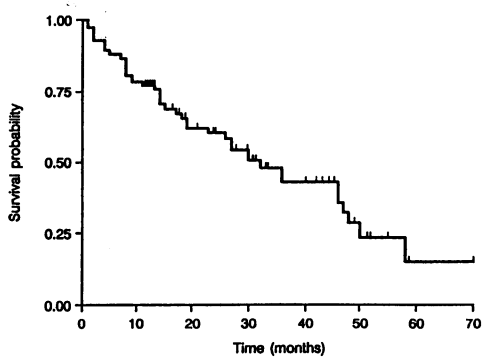

Fig 1. Survival curve for all 67 patients studied.

Fig 2 shows survival by stage. Stage III fared worse than stage I (median survivals 18 and 47 months respectively). Fig 3 shows the highly significant reduction in survival when the platelet count was $<100 \times 10^9/1$.

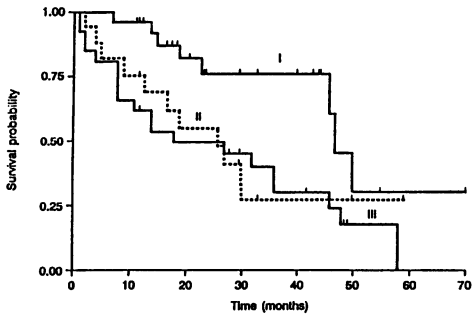

Fig 2. Survival curves for 67 patients, subdivided according to stage I, II, or III.

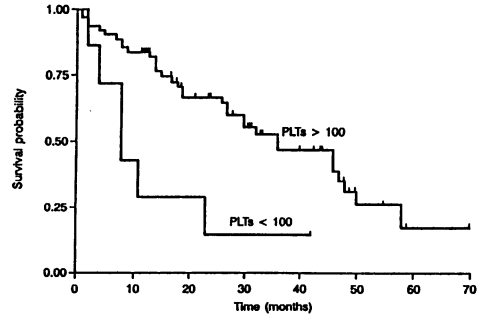

Fig 3. Survival curve for patients, subdivided according to platelet count (Plts) <100 and >100 ($\times 10^9/1$).

Table IV analyses the variables that were significant or approached significance as prognostic indicators. For categorical variables, the risk of each category relative to a reference category is shown — the relative risk of stage II compared to stage I was 2·6 and for stage III compared with stage I was 2·9. For a continuous variable the table shows the risk associated with a unit increase in that variable. For example, because serum creatinine was $\log_{10}$ transformed the relative risk of 2·4 is that associated with a tenfold increase in creatinine level. A 1·0 g increase in haemoglobin level is associated with a 21% reduction in the risk of death.

In the proportional hazard model, stage, age and platelet count were found to have independent prognostic significance. Although haemoglobin, creatinine and

TABLE IV

Relative risks of death from selected prognostic variables derived from univariate (log rank) and multivariate analyses of survival in 67 myeloma patients. 95% confidence limits in brackets

Variable	*Univariate results*		*Multivariate results*	
	Relative risk (95% CL)	*P*	*Relative risk (95% CL)*	*P*
Age				
> 70 yr vs < 70 yrs	1·8 (1·0–3·5)	0·062	2·7 (1·4–5·5)	0·005
Stage				
II vs I	2·6 (1·0–6·4)	0·024	3·6 (1·4–9·3)	0·003
III vs I	2·9 (1·3–6·7)		3·7 (1·6–8·9)	
Platelets ($\times 10^9$/l)				
< 100 vs > 100	0·3 (0·1–0·8)	0·006	0·4 (0·2–0·9)	0·037
Haemoglobin (g/dl)	0·8 (0·6–0·7)	0·004		
Creatinine (μmol/l) (log scale)	2·4 (1·0–5·8)	0·059		
Urea (mmol/l) (log scale)	3·7 (1·4–9·8)	0·015		

urea were individually significant they are already considered during staging. They do not therefore give additional prognostic significance when added to the model. In contrast to other studies[11] serum β_2 microglobulin levels (uncorrected for serum creatinine) were not found to be of prognostic significance but this measure was often not recorded in those patients who presented with advanced disease.

EARLY DEATHS

Eight patients died within six months of diagnosis. Of these, three were Stage IIa, two Stage IIIa and three Stage IIIb. One patient refused further admission to hospital and died at home two months after diagnosis. Three died of documented sepsis which was also strongly suspected as the cause of death of two others. One patient died of complications of renal failure and hypercalcaemia, and one from a probable pulmonary embolus. The number of hospital admissions for the 39 deceased patients ranged from 1 to 21 but with a median of 2 admissions during the course of their illness. The percentage of total time in hospital from diagnosis to death ranged from 0·5% to 100%, with a median 6·7%. Fifteen of the patients who died received at least one course of radiotherapy for palliation of bone pain during the course of their illness.

DISCUSSION

In general the diagnosis of myeloma is straightforward, but difficulties can arise during the early stages. Table V shows the minimal criteria for the diagnosis of myeloma from several centres.[5, 12, 13, 14] It is possible for example to meet the criteria for the diagnosis of myeloma and yet not be eligible for entry into the MRC V myeloma trial. Only about 15% of patients with myeloma are entered into trials co-ordinated by the MRC.[3]

TABLE V

Criteria for diagnosis of myeloma

Source	*A* *% Plasma cells in bone marrow*	*B* *Paraprotein level*	*C* *Osteolytic lesions*	*Minimal criteria for myeloma*
Chronic leukaemia myeloma task force[10]	>5% in marrow aspirate or other tissue	Monoclonal globulin	Osteolytic bone lesions	B+A or B+C
Hjorth[5]	>10%	IgG>30 g/l or IgG>20 g/l and/or BJ>1g/l	Osteolytic bone lesions	A+B or A+C
RA Kyle[11]	>10% abnormal immature plasma cells or histological proof of extramedullary plasmacytoma	M protein in serum (usually>30 g/l or in urine	Osteolytic lesions	A and usual clinical features of myeloma and either B or C
Maconduit[12]	>15% or infiltrates in biopsy	Associated M component	Not required	A+B
MRC V myeloma trial[4]	>20% or evidence of monoclonality if<20%	Band in blood or urine	Definite lytic lesions	Eligible for entry if any two of ABC
Belfast City Hospital	>5% in marrow aspirate	Monoclonal globulin	Lytic lesions	B+A or B+C

The present study, although encompassing a relatively small number of patients, was comprehensive in that it included all patients with myeloma (except two) diagnosed during a five year period. Comparison with the Nottingham unselected group[9] shows a slightly longer survival, which could be explained by the higher proportion of patients in the Nottingham study with poor prognostic features. Survival results from trials cannot be compared directly with those from unselected groups because of the exclusion of patients with unfavourable prognostic features. Such exclusions have been shown to have significant effects on survival results from trials.[5] Our results approximate to those of the MRC trials but it is not clear whether the patient populations are similar. Table III shows that the distribution of variables of individual prognostic significance is similar in trial patients and in our series, even though 19% of our patients are aged over 75. The Salmon-Durie

staging system suggests that a higher proportion of the MRC trial patients had advanced disease. Durie himself has questioned the wisdom of a staging system which gives undue importance to the presence of lytic lesions, which were demonstrated in 70% of trial patients and yet had limited prognostic significance on their own.[10] Differences in the interpretation of radiographic findings may be important as this is more subjective than the interpretation of the other paramaters used in staging, which could cause an apparent difference between our series and trial patients as judged by the staging system.

Eight of our patients had myeloma diagnosed at an early stage as an incidental finding. They were given various chemotherapeutic régimes; one died at 19 months from a ruptured abdominal aneurysm, the other seven remain alive and well at follow-up periods ranging from 12 to 70 months (median 40 months). While there have been no trials showing survival benefit from early treatment of myeloma, the experience with this small group of eight patients is encouraging. In the absence of a specific indication (such as bone plasmacytoma) such treatment remains a difficult decision.

In 1956 five year survival figures for myeloma averaged 5·6%.[15] There was an improvement following the introduction of melphalan and prednisolone about 1965. The recognition of the importance of infection and its improved treatment has also led to improved survival. There has been little further improvement despite the recent use of additional alkylating agents and anthracyclines. The VAD (vincristine, adriamycin, dexamethasone) regimen is very effective in relapsed and refractory myeloma but it has not been shown to improve survival when used in previously untreated patients.[16, 17] Indeed there is some evidence that the most important part of the VAD regimen is dexamethasone,[18] although the other agents contribute to its effectiveness.

Marrow ablative therapy with haemopoietic stem cell support has been shown recently to produce complete remission rates of 20–30%.[19, 20, 21, 22] Allogeneic bone marrow transplantation (from HLA matched donors) has been used in myeloma patients under 55 years of age. Of the typical population with myeloma, 75% would be excluded on the basis of age with a further reduction due to lack of HLA matched siblings. Gahrton[22] reported a mortality of 40% from treatment-related complications, which seems unacceptably high especially as most survivors ultimately relapse. Two-thirds of myeloma patients could be eligible for autologous bone marrow transplantation (using their own bone marrow) as mortality from this procedure has been shown not to increase up to age 70.[21] Recently it has been demonstrated that peripheral blood stem cells may be harvested following the use of chemotherapy and the cytokine granulocyte-colony stimulating factor (G-CSF).[23] The patient's bone marrow may be reconstituted using these peripheral blood stem cells avoiding the use of autologous marrow which may be contaminated with myeloma cells. The technique is limited as the yield of peripheral blood stem cells is much poorer in patients who have been heavily pretreated with chemotherapy or radiotherapy. The implication of these reports is that stem cell damage due to prolonged alkylating therapy should be avoided in potential candidates for autologous transplantation. Early assessment of suitability for such a procedure should be undertaken, ideally at the time of diagnosis, and peripheral blood stem cell harvest undertaken in the early stages of treatment, as is now the practice at this hospital.

Even though overall survival in myeloma may not have improved dramatically since the introduction of melphalan, much can now be done to palliate this devastating illness. The majority of patients have good quality survival and most are managed as outpatients. Recent developments such as the use of interferon to prolong plateau phase and the use of G-CSF to harvest peripheral blood stem cells and increase the safety of marrow transplantation suggest that further improvement in survival may now be obtainable.

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